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Association between lipoprotein (a) and risk of atherosclerotic cardiovascular disease events among maintenance hemodialysis patients in Beijing, China: a single-center, retrospective study

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Abstract

Background Serum lipoprotein(a) [Lp(a)] is an independent risk factor for atherosclerotic cardiovascular disease (ASCVD) in the general population, its association with ASCVD incidence in Chinese maintenance hemodialysis (MHD) patients remains unclear. We aimed to evaluate the relationship between Lp(a) levels and ASCVD incidence among MHD patients in Beijing, China.

Methods This retrospective, observational cohort study included MHD patients at Beijing Tongren Hospital from January 1, 2013 to December 1, 2020, and followed until December 1,2023. The primary outcome was ASCVD occurrence. Kaplan-Meier survival analysis was used to evaluate ASCVD-free survival in MHD patients, with stratification based on Lp(a) levels. Cox regression analyses were conducted to assess the association between Lp(a) levels and the occurrence of ASCVD.

Results A total of 265 patients were enrolled in the study. The median follow-up period were 71 months.78 (29.4%) participants experienced ASCVD events, and 118 (47%) patients died, with 58 (49.1%) deaths attributed to ASCVD. Spearman rank correlation analyses revealed positive correlations between serum Lp(a) levels and LDL-c levels, and negative correlations with hemoglobin, triglyceride, serum iron, serum creatinine, and albumin levels. Multivariate Cox regression analysis showed that Lp(a) levels ≥ 30 mg/L, increased age, decreased serum albumin levels, and a history of diabetes mellitus were significantly associated with ASCVD incidence.

Conclusions This study demonstrated an independent and positive association between serum Lp(a) levels and the risk of ASCVD in MHD patients, suggesting that serum Lp(a) could potentially serve as a clinical biomarker for estimating ASCVD risk in this population.

Keywords Lipoprotein (a), Atherosclerotic cardiovascular disease, Cardiovascular disease, End-stage renal disease, Maintenance hemodialysis

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Introduction

Lipoprotein (a) (Lp(a)) is a complex particle present in human plasma. Its structure closely resembles that of low-density lipoprotein (LDL), but it is distinguished by the presence of a specific glycoprotein called apolipoprotein(a) [apo(a)] [1–4]. This glycoprotein is similar to plasminogen and is covalently linked to apolipoprotein B-100 through a disulfide bond. Lp(a) plays a role in promoting arteriosclerosis and blood coagulation [4–8]. Lp(a) has been observed in atherosclerotic lesions of saphenous vein bypass grafts and native coronary arteries, distributed similarly to LDL. In the general population, elevated levels of Lp(a) are an independent risk factor for atherosclerotic cardiovascular diseases (ASCVD) due to mechanisms associated with increased atherogenesis, inflammation, and thrombosis [9–11].

ASCVD mortality is the leading cause of death, among individuals undergoing hemodialysis, with a mortality rate at least 10 times higher than that of the general population [9, 12, 13]. Additionally, 40% of end-stage renal disease (ESRD) patients have CVD at the initiation of dialysis, and the risk for recurrent ASCVD events is likely to be much higher [14, 15]. However, the research findings on the correlation between Lp(a) and ASCVD risk among ESRD patients are inconsistent [16–19].

On the other hand, Lp(a) concentrations have been observed to exhibit racial disparities, surpassing those of any other cardiovascular biomarker [10, 20–22]. Limited research has been conducted on the correlation between Lp(a) and the risk of ASCVD in the Chinese population undergoing hemodialysis. The present retrospective study analyzed the association between serum Lp(a) and the risk of ASCVD in a longitudinal cohort of patients treated with maintenance hemodialysis (MHD), with a median follow-up of 71 months.

Patients and methods

Study population

This retrospective, observational cohort study included all patients who underwent maintenance hemodialysis (MHD) at Capital Medical University, Beijing Tongren Hospital from January 1, 2013 to December 1, 2020, and followed until December 1,2023. Eligible subjects were aged 18 years or older at the start of MHD and survived for at least 90 days from their initial hemodialysis therapy. Patients who underwent renal transplantation or peritoneal dialysis (PD), were excluded. Before starting the study, all participants signed informed consent forms, wherein they were informed that the research would entail collecting their medical information without including any personal details. The medical data obtained from participants was exclusively used for research purposes and was securely stored to maintain confidentiality and prevent any unauthorized disclosure. The study protocol was approved by the institute's ethics committee of Beijing Tongren Hospital. The ethics approval number for this study is TREC2024-KY110.

Data collection and measurements

Baseline demographic data, including age, gender, complications, and medication use, were obtained from the patients' medical records. Biochemical data at baseline, including Lp(a), Kt/V, urea reduction ratio (URR), leukocyte counts(WBC), hemoglobin, serum creatinine, blood urea nitrogen (BUN), serum uric acid, serum albumin, corrected serum calcium, serum phosphate, intact parathyroid hormone (PTH) values, serum iron, ferritin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and C-reactive protein (CRP), were assessed in the biochemical laboratory of Capital Medical University, Beijing Tongren Hospital. The concentrations of plasma TG, TC, LDL-c, HDL-c, serum creatinine, BUN, uric acid, and serum albumin were measured using an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan). All laboratory testing were in accord with standard biochemical analysis procedures. Lp(a) was measured on a Siemens Atellica (Siemens, Munich, Germany) platform and using the immunoturbidimetric Denka Seiken developed Roche 2nd generation assay (Roche Professional Diagnostics, Rotkreuz, Switzerland) with minimal apolipoprotein(a) isoform size bias. The intraassay coefficient of variation was ≤10%. A threshold of 30 mg/dL was used to classify patients into an elevated Lp(a) group and a normal Lp(a) group. Corrected serum calcium=calcium+0.8×(4 − serum albumin). URR = (BUN before dialysis-BUN after dialysis)/BUN before dialysis. Kt/V was calculated according to the second-generation formula of Daugirdas [23]. All data were obtained within three months after the initiation of hemodialysis.

Outcomes

The primary outcome of this study was the occurrence of atherosclerotic cardiovascular disease (ASCVD) during the follow-up period. ASCVD was defined as a composite outcome including hospitalization for myocardial infarction (MI), hospitalization for ischemic stroke, hospitalization for peripheral artery disease (PAD), death due to coronary heart disease (CHD), or death due to stroke. Incident cases of ASCVD were identified using death certificate data and hospital record linkage. To confirm the occurrence of study outcomes, medical records were reviewed and validated by three nephrologists in our HD center. MI hospitalization was defined based on symptoms, levels of cardiac biomarkers, and electrocardiograms consistent with acute myocardial ischemia. Ischemic stroke hospitalization was defined based on

sudden neurological symptoms and neuroimaging consistent with acute cerebral infarction. PAD hospitalization was defined based on peripheral artery bypass or angioplasty, or major amputation due to occlusive PAD. Deaths were identified through the retrieval of death certificates, as well as hospital and outpatient records.

Statistical analysis

Results were reported as mean ± standard deviation (SD) or median and interquartile range, depending on the distribution of the data, for continuous variables. Categorical variables were expressed as frequencies. Statistical analyses were performed using SPSS 23 for Windows (SPSS, Inc., Chicago, IL, USA). ANOVA analysis was used to compare groups for normally distributed continuous variables, while nonparametric tests were used for non-normally distributed variables. The chi-square test was utilized for categorical variables. Spearman correlation was used to assess the relationship between Lp(a) levels and baseline clinical parameters. Kaplan-Meier survival analysis was used to evaluate ASCVD-free survival in MHD patients, with stratification based on Lp(a) levels. Cox regression analyses were conducted to assess the association between Lp(a) levels and the occurrence of ASCVD. To assess the proportional hazards assumption in the Cox regression models, each covariate was transformed into a time-dependent covariate x*ln(t) and simultaneously included in the single-factor Cox regression equation. Covariates with P-values above 0.05 were considered to meet the assumption and included in the model. However, for covariates such as age with P-values < 0.05, further stratified analysis was performed to ensure compliance with the proportional hazards assumption before reintroducing them into the Cox regression model. Missing data were handled using multiple imputation techniques to minimize bias and ensure study validity. Statistical significance was defined as $p < 0.05$.

Results

A total of 290 patients undergoing MHD at dialysis center of Beijing Tongren Hospital, since January 1, 2013 to December 1, 2020. Of 290 MHD patients, 25 patients were transferred to transplantation. Thus, a total of 265 MHD patients were eligible for the study. The baseline characteristic data of patients are shown in Table 1. The mean age of the study participants was 63.78 ± 14.89 years, with 176 (66.4%) being men. Among the participants, 102(38.5%)had higher Lp(a) levels (≥ 30 mg/dL), and these individuals were more likely to have lower hemoglobin and serum iron levels. Compared to the normal Lp(a) group, the elevated Lp(a) group exhibited

Table 1 Baseline characteristics of MHD patients

	Lp(a)<30 mg/dL	Lp(a) ≥ 30 mg/dL	*P*-value
N	163(61.5%)	102(38.5%)	
Male (*N*,%)	104(63.8%)	72(70.6%)	0.286
Age(y)	63.05 ± 15.77	64.92 ± 13.36	0.308
Hemoglobin(g/L)	111.26 ± 12.91	105.17 ± 20.00	0.003*
Hct(%)	31.60 ± 11.06	26.92 ± 13.29	0.003*
WBC(*10^9/L)	6.49 ± 1.81	6.59 ± 2.22	0.705
serum creatinine(umol/L)	894.60 ± 308.59	813.01 ± 294.91	0.037*
Uric acid(umol/L)	410.05 ± 91.93	409.93 ± 99.45	0.992
Blood glucose(mmol/L)	7.31 ± 3.40	7.69 ± 4.11	0.423
Serum phosphorus(mmol/L)	1.96 ± 0.60	1.86 ± 0.60	0.175
Serum Calcium(mmol/L)	2.24 ± 0.23	2.20 ± 0.22	0.234
PTH (pg/ml)	311.05[155.6,609.68]	258.40[102.43,547.85]	0.196
Serum albumin(g/L)	38.67 ± 4.07	36.62 ± 5.45	0.001*
CRP (mg/L)	3.89[1.30,11.01]	5.08[1.43,16.43]	0.224
TC (mmol/L)	3.91 ± 0.82	4.04 ± 1.00	0.271
TG (mmol/L)	2.02 ± 1.38	1.87 ± 1.77	0.477
LDL-c (mmol/L)	2.14 ± 0.65	2.31 ± 0.82	0.088
Serum iron (umol/L)	12.82 ± 5.85	10.48 ± 5.23	0.007*
Serum ferritin (ng/ml)	150.10[69.8,394.55]	209.85[64.15,432.18]	0.283
Kt/V	1.32 ± 0.29	1.29 ± 0.31	0.560
URR (%)	65.81 ± 9.19	66.32 ± 9.85	0.676
History of Diabetes mellitus	65(40.0%)	62(60.8%)	0.027*
History of ASCVD	76(46.6%)	49(48.0%)	0.169
History of Hypertension	147(90.2%)	92(90.2%)	0.666
Statins use	55(33.7%)	57(55.9%)	0.041*

Table 2 Baseline characteristics of MHD patients categorized by lp(a) quartiles

	Q1	Q2	Q3	Q3
N	66(24.9%)	66(24.9%)	66(24.9%)	67(25.3%)
Male(*N*,%)	43 (65.2%)	44(66.7%)	49(74.2%)	40(62.0%)
Age(y)	59.87 ± 15.68	64.72 ± 15.53	65.93 ± 14.48	64.76 ± 13.17
Hemoglobin(g/L)	112.34 ± 14.07	110.45 ± 10.82	109.77 ± 17.12	102.44 ± 20.57
Hct (%)	33.39 ± 10.55	31.94 ± 7.90	26.39 ± 15.16	27.02 ± 12.64
WBC(*10^9/L)	6.50 ± 1.77	6.56 ± 1.85	6.24 ± 1.87	6.84 ± 2.37
serum creatinine(umol/L)	905.16 ± 322.74	887.77 ± 302.74	862.93 ± 297.00	789.39 ± 291.96
Uric acid(umol/L)	410.86 ± 99.90	417.50 ± 75.34	404.56 ± 101.22	407.16 ± 100.91
Blood glucose(mmol/L)	7.97 ± 3.17	7.09 ± 2.85	6.78 ± 2.88	8.33 ± 4.71
Serum phosphorus(mmol/L)	1.96 ± 0.57	2.01 ± 0.69	1.83 ± 0.60	1.89 ± 0.65
Serum Calcium(mmol/L)	2.24 ± 0.23	2.24 ± 0.25	2.21 ± 0.21	2.19 ± 0.22
PTH (pg/ml)	340.30[145.70, 611.40]	294.4[140.0, 609.10]	277.45[119.85, 605.18]	292.80[102.43,540.43]
Serum albumin(g/L)	39.27 ± 3.74	38.33 ± 4.36	37.25 ± 5.31	36.45 ± 5.24
CRP (mg/L)	3.37[1.34,8.92]	3.22[1.20,11.24]	5.77[1.17,16.73]	4.73[2.02,14.87]
TC (mmol/L)	3.88 ± 0.85	4.00 ± 0.75	3.83 ± 0.93	4.15 ± 1.02
TG (mmol/L)	2.25 ± 1.66	1.91 ± 1.15	1.77 ± 1.38	1.90 ± 1.90
LDL-c(mmol/L)	2.01 ± 0.66	2.27 ± 0.58	2.17 ± 0.77	2.41 ± 0.83
Serum iron(umol/L)	14.04 ± 6.09	11.97 ± 5.54	10.44 ± 4.23	10.88 ± 6.12
Serum ferritin(ng/ml)	161.50[52.08,417.30]	153.35[74.48, 371.63]	179.35[86.93,366.65]	215.60[71.80,438.15]
Kt/V	1.29 ± 0.31	1.34 ± 0.28	1.31 ± 0.28	1.30 ± 0.32
URR (%)	65.86 ± 9.52	65.27 ± 9.91	66.14 ± 8.49	66.83 ± 10.01
History of Diabetes mellitus	26(39.4%)	32(48.5%)	37(56.1%)	32(47.8%)
History of ASCVD	33 (50.0%)	28(42.4%)	28(42.4%)	36(53.7%)
History of Hypertension	60(90.9%)	64(97.0%)	58(87.9%)	57(85.1%)
Statins use	23(33.3%)	24(36.3%)	28(42.4%)	37(55.2%)

Table 3 Spearman correlation analysis of lp(a) levels and other measurements

Variable	*R*	*P*-value
Hemoglobin(g/L)	-0.189	0.000
Serum creatinine(umol/L)	-0.140	0.025
Serum albumin(g/L)	-0.215	0.001
Triglyceride (mmol/L)	-0.147	0.022
LDL-c (mmol/L)	0.139	0.032
Serum iron(umol/L)	-0.289	0.000

significantly lower serum albumin and lower serum creatinine. There were no significant differences in the prevalence of hypertension and ASCVD among the baseline characteristics. The median concentration of Lp(a) was 19.5 mg/dL, with the 25th and 75th percentiles being 10.2 and 42.3 mg/dL, respectively. The participants were categorized by quartiles based on their Lp(a) levels, and the baseline data are presented in Table 2.

Spearman rank correlation analyses revealed that serum Lp(a) levels positively correlated with LDL-c levels and negatively correlated with hemoglobin, triglyceride, serum iron, serum creatinine, and albumin levels ($P<0.05$) (Table 3).

During a median follow-up period of 71 months (interquartile[IQR] 36–119), 78(29.4%)participants experienced ASCVD events. These events consisted of 49 cases of MI, 17 cases of ischemic stroke, and 12 cases of PAD. Additionally, 118 (44.5%) patients died, with 45 (38.1%) attributed to cardiovascular disease (CVD), 13 (11.0%) to stroke, 7 (5.9%) to malignant tumors, 38 (32.2%) to infection, 2 (1.7%) to gastrointestinal bleeding, 5 (4.2%) to malnutrition, and 6 (5.1%) to other causes.

The percentage of patients free from ASCVD at the first, third, and fifth year of follow-up were as follows: in the normal Lp(a) group, 96.1%, 91.9%, and 85.1%; in the elevated Lp(a) group, 89%, 72.8%, and 60.4%. Patients in the elevated Lp(a) group exhibited a lower cumulative ASCVD-free survival rate (log-rank test $\chi2=38.46$, $p=0.000$) compared to those in the normal Lp(a) group (Fig. 1).

Univariate Cox regression analyses revealed that a history of diabetes mellitus, decreased Hct levels, Lp(a)≥30 mg/L, higher fasting blood-glucose levels, elevated uric acid (UA) levels, higher phosphorus levels, lower serum albumin levels, and an inflammatory status were significantly associated with an increased incidence of ASCVD. Based on these univariate findings, multivariate Cox regression analyses were conducted to further investigate the risk factors associated with ASCVD. The results showed that Lp(a) levels≥30 mg/L, increased age, decreased serum albumin levels, and a history of diabetes mellitus were significantly associated with the incidence of ASCVD (Table 4). To further explore the relationship between Lp(a) and ASCVD under different conditions,

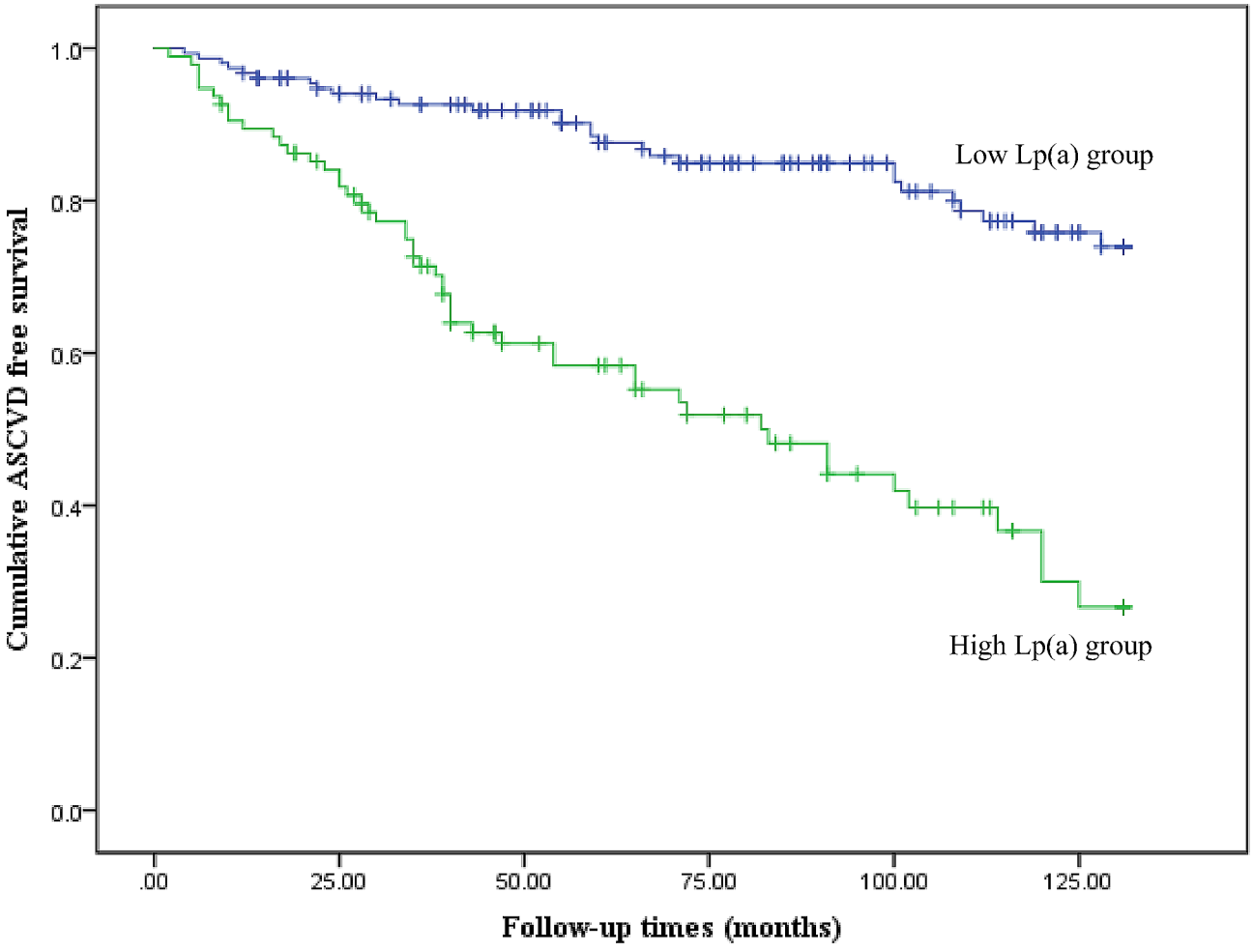

Fig. 1 Subgroups analysis of Lp(a) with ASCVD incidence

a stratified univariate Cox regression analysis was performed to assess the association between elevated Lp(a) levels and the risk of ASCVD. The study population was stratified based on albumin levels, history of diabetic mellitus, history of ASCVD, age, statin in use, and gender. Figure 2 illustrated a significant association between lipoprotein(a) levels≥30 mg/dL and an elevated incidence of ASCVD, irrespective of history of ASCVD at baseline, history of diabetes status, and statin use. However, the impact of Lp(a) on ASCVD risk appeared to be attenuated in the subgroup with albumin levels below 35 g/L (HR 5.37[0.94–2.24], $P=0.071$). Table 5 presented the results of the association between lipoprotein(a) levels and the risk of ASCVD events after adjusting for various confounding factors. The analysis revealed that individuals with Lp(a) levels≥30 mg/dL had a significantly increased risk of ASCVD (HR 17.84 [4.03–78.97], $P=0.000$) even after accounting for factors such as age, gender, disease history, statin use history, clinical data, and dialysis adequacy index. Furthermore, it found that for every 1 mg/L increase in Lp(a) levels, there was a corresponding increase in the risk of ASCVD events even after adjusting for multiple confounding factors.

Discussion

This study aimed to investigate the relationship between serum Lp(a) levels and the incidence of ASCVD in Chinese MHD patients. Our findings indicated that a high serum Lp(a) level is an independent predictor of incident ASCVD in MHD patients.

The kidney has been shown to play a role in the degradation of Lp(a), as evidenced by the impact of chronic kidney disease on Lp(a) levels, the presence of apo(a) fragments in urine, and the difference in Lp(a) concentrations between arterial and venous blood in the renal circulation [8]. Several studies have demonstrated that Lp(a) levels increase as renal function declines [24, 25].

A large-scale meta-analysis involving 126,634 participants and 1.3 million person-years of follow-up has confirmed previous findings that identified an inflection point for the risk of myocardial infarction at Lp(a) levels exceeding 30 mg/dL [1, 26]. The 2016 Canadian

Table 4 Univariate and multivariate Cox regression models

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Male	1.11(0.87–1.41)	0.412		
Lp(a) ≥ 30 mg/dL	4.29(2.69–6.85)	0.000	4.47 (2.16–9.22)	0.000
Age, per 10 years	1.54(1.30–1.82)	0.000	1.46(1.05–2.03)	0.025
Hct (%), per unit	0.97(0.95–0.98)	0.000		
TC (mmol/L), per unit	1.02(0.79–1.32)	0.887		
LDL-c (mmol/L), per unit	1.08(0.79–1.48)	0.618		
TG (mmol/L), per unit	0.85(0.69–1.04)	0.110		
Uric acid (umol/L), per unit	1.00(0.99-1.000)	0.039		
Blood Fasting-glucose (mmol/L), per unit	1.07(1.02–1.13)	0.009		
Phosphorus(mmol/L), per unit	0.53(0.34–0.79)	0.002		
Calcium(mmol/L), per unit	0.83(0.30–2.25)	0.712		
Serum albumin(g/L), per unit	0.89(0.85–0.92)	0.000	0.90(0.82–0.98)	0.015
Serum iron (umol/L), per unit	0.92(0.86–0.99)	0.017		
Ferritin(ng/ml), per unit	1.001(1.000-1.002)	0.020		
CRP (mg/L), per unit	1.01(1.00-1.02)	0.011		
Kt/V, per unit	1.07(0.45–2.52)	0.885		
URR, per unit	0.99(0.97–1.02)	0.546		
History of Diabetes mellitus	3.09(1.51–6.35)	0.002	3.38(1.54–7.41)	0.002
History of Hypertension	1.84(0.25–13.5)	0.547		
History of ASCVD	2.22(0.99–4.44)	0.550		
Statins use	2.66(1.30–5.45)	0.007		

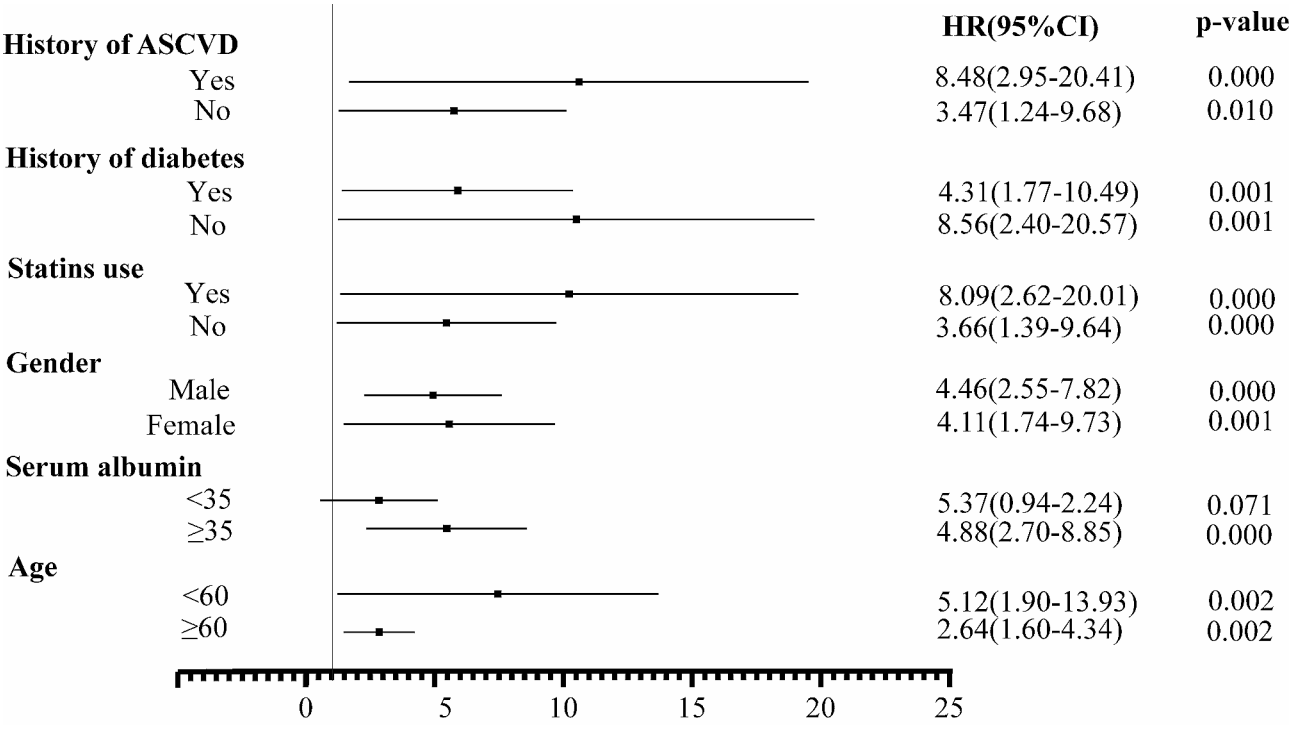

Fig. 2 Kaplan-Meier survival analysis of ASCVD-free status in MHD patients with different serum Lp(a) levels

Cardiovascular Society Guidelines for the Management of Dyslipidemia consider Lp(a) greater than 30 mg/dL to be a risk factor for CAD [27]. Similarly, the 2023 Chinese Guidelines for Lipid Management indicate that Lp(a) levels above 30 mg/dL increase the risk of ASCAD [28]. In our study, a threshold of 30 mg/dL was used to classify patients into an elevated Lp(a) group and a normal Lp(a) group. Previous research has reported that

Table 5 The associations between serum lp(a) levels and risk of ASCVD

		HR	95%CI	*P* value
Model 1[a]	Continuous Lp(a)[d]	1.02	1.01–1.02	0.000
	Lp(a) ≥ 30 mg/dL[e]	4.29	2.69–6.85	0.000
Model 2[b]	Continuous Lp(a)	1.02	1.01–1.04	0.001
	Lp(a) ≥ 30 mg/dL	4.45	2.08–9.53	0.000
Model 3[c]	Continuous Lp(a)	1.05	1.02–1.08	0.000
	Lp(a) ≥ 30 mg/dL	17.84	4.03–78.97	0.000

a. Model 1. Unadjusted

b. Model 2. Adjusted for age, gender, hypertension history, diabetic mellitus history, ASCVD history, statins use

c. Model 3. Adjusted for age, gender, hypertension history, diabetic mellitus history, ASCVD history, statins use, hemoglobin, WBC, serum glucose, serum phosphorus, serum calcium, TC, TG, LDL-c, ferritin, serum iron, PTH, Kt/V, URR, CRP

d. Continuous Lp(a): per 1 mg/dL higher Lp(a)

e. Lp(a)<30 mg/dL as reference

the proportion of elevated Lp(a) in the general population is approximately 12-20.3% [29]. However, our study revealed that in the MHD population, this proportion reaches 38.5%, suggesting higher levels of Lp(a) in MHD patients compared to the general population.

In MHD patients, Lp(a) levels were found to inversely correlate with serum creatinine and albumin concentrations prior to hemodialysis sessions. Serum creatinine and albumin are commonly used as markers of nutritional status in this patient population. This inverse association suggests that MHD patients with suboptimal nutritional status may exhibit higher Lp(a) concentrations. Physiologically, diminished albumin levels may instigate an upregulation in the synthesis of apolipoprotein B (apo[B])-containing lipoprotein particles, including Lp(a), thereby contributing to their elevated levels [30, 31]. Notably, there was no correlation between Lp(a) levels and the adequacy indicators of hemodialysis, namely KT/V and URR, suggesting that conventional hemodialysis techniques are ineffective in removing Lp(a).

Furthermore, Lp(a) was positively correlated with LDL-c levels and negatively correlated with TG levels. Interestingly, we found a significantly higher proportion of statins in the group with elevated Lp(a) compared to the normal group. Previous studies have reported that statins can increase Lp(a) levels by 10–20% [1], which may explain why some patients do not respond well to statin therapy in terms of lowering LDL-c levels, as their cholesterol may primarily be present in Lp(a) rather than LDL particles [32]. Statins induce upregulation of LDL receptors (LDLR), however, the role of the LDLR in Lp(a) clearance is minor [33], on the other hand, statin treatment increased LPA expression and apolipoprotein(a) production and secretion [34]. The mechanism of Lp(a) cellular uptake remains unclear, with other receptors such as macrophage scavenger receptors, megalin receptors, asialoglycoprotein receptors being considered to be involved in Lp(a) uptake. The capacity of macrophages to uptake Lp(a) is crucial, as the excessive uptake of lipoproteins by macrophages, leading to their transformation into foam cells, is a major mechanism of atherogenesis [35]. Similar to LDL-c, Lp(a) does not originate from the catabolism of another lipoprotein. In individuals with elevated triglyceride levels, Lp(a) is reduced, likely due to increased plasma lipoprotein clearance [36]. In the present study, elevated Lp(a) levels were found to be a risk factor for ASCVD events, independent of statin use. Univariate cox regression analyses showed that statin use was associated with an increased ASCVD risk, while multivariate cox regression analysis showed the association was not significant after adjusting for Lp(a) levels.

Elevated levels of Lp(a) have been associated with a negative impact on iron metabolism, often leading to lower serum iron and hemoglobin levels. This inverse relationship may stem from the inflammatory role of Lp(a), which can activate the NF-κB pathway in monocytes, and increase inflammation [4, 37–39]. Heightened inflammation can affect hepcidin levels, a master regulator of iron homeostasis, leading to disturbances in iron metabolism and an increased risk of anemia, especially in conditions such as maintenance hemodialysis (MHD) [40]. Thus, Lp(a) may be indirectly contributing to iron utilization impairment and anemia.

Previous studies have shown that high levels of Lp(a) are associated with the progression of atherosclerosis and an increased risk of ASCVD events in the general population [29]. However, the research findings on the role of Lp(a) in relation to incident ASCVD among patients with renal failure are inconclusive and contradictory. Koda et al [41] conducted a study on Japanese hemodialysis patients and found that those with Lp(a) values ≥ 30 mg/dl had a significantly higher risk of cardiovascular mortality (RR 3.93). Xu et al [16] reported that high serum Lp(a) levels were associated with an increased risk of death from cardiovascular events in peritoneal dialysis patients. However, another study involving 440 hemodialysis patients did not find a significant association between Lp(a) levels and outcomes related to coronary artery disease [17]. Similarly, Poudel et al [18] found no association between Lp(a) and the risk of recurrent ASCVD events in adults with CKD. Additionally, a retrospective study investigated the predictive value of baseline serum Lp(a) levels for subsequent stroke and found that higher levels were associated with a lower risk of hemorrhagic stroke [19].

At the initiation of hemodialysis, we conducted a baseline assessment that showed no significant difference in the prevalence of ASCVD among patients irrespective of their serum Lp(a) levels. However, as the study progressed, we observed a significant difference in the

incidence rate of ASCVD between patients with elevated Lp(a) levels and those with normal levels during the follow-up period. Notably, patients with elevated Lp(a) levels had a higher incidence rate of ASCVD compared to those with normal levels. This highlights the potential of Lp(a) as a prognostic marker for cardiovascular risk among the hemodialysis population.

Furthermore, the multivariate Cox regression analyses showed that demonstrated significant associations between increased age, decreased serum albumin levels, a history of diabetes mellitus, and the incidence of ASCVD. Diabetes has been widely recognized as a conventional risk factor for ASCVD [8], particularly in individuals with MHD [42, 43].

Previous studies have reported a higher prevalence of malnutrition and inflammation in patients with CKD [44].Proinflammatory cytokines and malnutrition play a crucial role in the development of atherosclerosis in ESRD [45]. Univariate Cox regression analyses revealed that lower serum albumin levels and higher CRP levels were associated with an increased incidence of ASCVD during the follow-up period. After adjusting for other confounding factors, the multivariate Cox regression analysis indicated that hypoproteinemia is a significant risk factor for ASCVD. Furthermore, Lp(a) was not identified as a risk factor for ASCVD in individuals with serum albumin levels < 35 g/L, whereas it remained a significant predictor of ASCVD in those with normal serum albumin levels. This suggests that albumin as a crucial mediator in the relationship between Lp(a) and ASCVD. Firstly, Serum albumin plays a pivotal role in lipoprotein metabolism, encompassing processes such as synthesis, secretion, and clearance [46]. Decreased serum albumin levels have been associated with elevated Lp(a) levels, potentially attenuating the predictive capacity of Lp(a) for ASCVD. Secondly, low albumin levels may reflect poor nutritional status or the presence of other underlying diseases, which may be related to ASCVD risk and not solely influenced by Lp(a). Additionally, low albumin levels may be associated with other inflammatory factors or metabolic abnormalities that could also influence the development and progression of ASCVD, making the link between lipoprotein(a) and ASCVD risk less evident.

Several limitations should be acknowledged in the present study. Firstly, the study focused exclusively on the Chinese Han population in a single center. Conducting a multi-center study would improve the generalizability of the results by including diverse populations from different regions, providing a more comprehensive understanding of the association between Lp(a) levels and ASCVD risk in MHD patients. Secondly, although Lp(a) was measured using the immunoturbidimetric Denka Seiken developed Roche 2nd generation assay with minimal apolipoprotein(a) isoform size bias, our study did not measure apo(a) isoforms in the study population. It potentially introduced bias into our results because apo(a) isoforms are associated with Lp(a) concentration and can partly predict ASCVD risk. However, recent research suggests that circulating plasma Lp(a) concentration is a more accurate predictor of ASCVD risk than apo(a) isoform size or variations within the LPA gene locus [3, 47]. Mendelian randomization studies also indicate that reducing Lp(a) concentration may be beneficial in preventing ASCVD, as shown by Gudbjartsson et al. highlighting the superiority of circulating plasma Lp(a) concentration as a predictor of ASCVD risk compared to apo(a) isoform size [48]. Lastly, it is essential to acknowledge that the retrospective observational design of our study limits our ability to establish causal relationships based on the findings. To further clarify the relationship between Lp(a) levels and ASCVD events, we recommend conducting a prospective cohort study in the future.

Conclusions

The present study demonstrated an independent and positive association between serum Lp(a) levels and the risk of ASCVD in patients undergoing MHD. These findings suggest that serum Lp(a) could potentially serve as a clinical biomarker for estimating the risk of ASCVD in HD-treated patients.

Abbreviations

ASCVD	Atherosclerotic cardiovascular diseases
BUN	Blood urea nitrogen
CRP	C-reactive protein
HDL	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein a
MHD	Maintenance hemodialysis
TC	Total cholesterol
TG	Triglycerides
UA	Uric acid
URR	Urea reduction ratio
PTH	Intact parathyroid hormone

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Not applicable.

Author contributions

Guojuan Zhang was responsible for the study conception and design and critically reviewed the final manuscript. Qiaojing Liang and Liping Jiang was responsible for data acquisition, analysis, interpretation of data, initial drafting and revising the manuscript. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability

The datasets analyzed in the current study are not publicly available to ensure privacy of research participants and comply with regulations of the ethics approval. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study is in conformity with the Helsinki and Istanbul declarations and its amendments. The study was approved by the Ethics Committee of Beijing Tongren Hospital. The ethics approval number for this study is TREC2024-KY110. Before starting the study, all participants signed informed consent forms, wherein they were informed that the research would entail collecting their medical information without including any personal details. The medical data obtained from participants was exclusively used for research purposes and was securely stored to maintain confidentiality and prevent any unauthorized disclosure.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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